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Cancer Investigation

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NEW DRUGS

Taxanes: A New Class of Antitumor Agents

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ABSTRACT

Taxanes belong to a new group of antineoplastic agents with a novel mechanism of action for a cytotoxic drug. They promote microtubule assembly and stabilize the microtubules. Paclitaxel, the first agent in this group to become available, was isolated from the Pacific yew, Taxus brevifolia, in 1971. In preclinical and clinical studies, paclitaxel and its semisynthetic analog docetaxel exhibit significant antitumor activity. This review deals with the physicochemical properties, pharmacology, and results of preclinical and clinical trials of the taxanes.

INTRODUCTION

The history of paclitaxel started around the turn of the century, when a British official in the Indian subcontinent noted that parts of the European yew, *Taxus baccata*, were used in a clarified butter preparation for the treatment of cancer (1). Much later, in 1962, crude bark extracts of the related Pacific (or western) yew, *Taxus brevifolia*, were provided to the National Cancer Institute (NCI, USA) by the U.S. Forest service, as part of a NCI program to evaluate U.S. plants for anticancer activity. The crude alcohol extract was shown to be cytotoxic against several murine tumours. In 1971, Wani et al. reported the isolation and characterization of paclitaxel, the active component in the extract (2). Because of scarcity of the crude material and difficulty in developing a suitable clinical intravenous (i.v.) pharmaceutical formulation, and the belief that the mechanism of action of paclitaxel was identical to that of the vinca alkaloids, further development of paclitaxel was delayed in the 1970s. However, when its unique mechanism of cytotoxic action was unraveled, the interest in paclitaxel rekindled. In 1979, Horwitz and colleagues reported that paclitaxel acts as a promotor of microtubule assembly in vitro and shifts the physiological equilibrium between tubulins and microtubule toward polymerization (3). Disturbance of this dynamic physiological process may explain paclitaxel-induced cytotoxicity. This is a novel mechanism of action for a cytotoxic drug and contrasts with the action of other antimicrotubule agents (e.g., vinca alkaloids, colchicine), which induce depolymerization of microtubules.

Under the auspices of the NCI, preclinical studies were conducted and clinical trials were initiated. Activity against metastatic ovarian cancer, malignant melanoma, non-small cell lung cancer, small cell lung cancer, and breast cancer was demonstrated. Reviews of preclinical and clinical data of paclitaxel were published by Rowinsky et al. (4,5) in 1990 and 1992 and by Chabner in 1991 (6).

Docetaxel (Taxotere®; NSC 628503), a semisynthetic analog of paclitaxel (Taxol®; NSC 125973) has a similar mechanism of action and clinical activity (7). In this review paclitaxel and docetaxel chemistry and pharmacology will be discussed, followed by an evaluation of the preclinical and clinical data currently available.

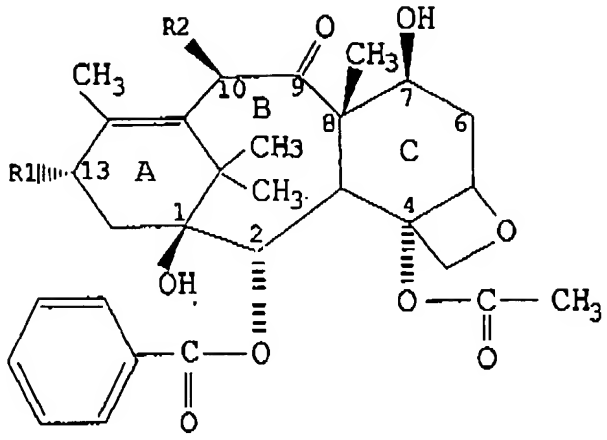
PHYSICOCHEMICAL AND PHARMACEUTICAL PROPERTIES

Origin and Isolation

Paclitaxel was first isolated from the bark of the Western yew, *T. brevifolia*, and characterized by Wani et al. in 1971 (2). This tree with a height of 15–50 ft (4–15 m), is native to Western North America. Related species are found in Canada, the Himalayas, Europe, and Russia. The Western yew is of minor commercial use. The wood is used by North American natives to make bows and canoe paddles, and many *Taxus* species, are cultivated as ornamental plants (8,9). Isolation of the active substance is performed by making an alcohol extract of the stem bark and partitioning this between water and chloroform. The chloroform extract is further fractionated using chromatographic techniques. Fractionation was guided initially by establishment of cytotoxic activity in several (biological) assays (e.g., 9KB culture systems and murine L1210, P385, and P1534 leukemias). Large-scale isolation is based on the same method but guided by high-performance liquid chromatography (HPLC). One of the problems in isolation is the separation of paclitaxel and cephalomannine, a related taxane present in significant quantities. These compounds show close structural similarities (Fig. 1). Efficient separation can be achieved by an HPLC method, reported by Cardellina (10). This system uses normal-phase HPLC on a cyanopropyl column with an eluent comprised of hexane/isopropanol (2:1) with ultraviolet (UV) detection at 270 nm. Paclitaxel and cephalomannine show retention times of 45.3 min and 38.1 min, respectively. Harvey et al. (11) described a reversed-phase HPLC system also accomplishing separation of both taxanes. In this system, a microcolumn packed with octadecylsilica material was utilized with an eluent consisting of methanol-water-acetonitrile (3:3:4). Paclitaxel showed a retention time of 61.2 min and cephalomannine of 57.5 min. The components were detected by their UV absorbance at 225 nm.

Huge amounts of material are needed in production of paclitaxel (10,000 kg bark yields 1 kg of pure paclitaxel); several other sources have, therefore, been sought. To date, large-scale total chemical synthesis of paclitaxel appears not feasible, because of its complex structure. Intensive research efforts are focused on other biological sources of paclitaxel.

Several studies have shown that needles of other species of the genus *Taxus* contain amounts of paclitaxel comparable to that isolated from the stem bark of *T. brevifolia*. The needles of *Taxus media cv hicksii* contain the highest amounts of both 10-deacetylbaccatin III (Fig. 1) and paclitaxel (12). 10-Deacetylbaccatin III is a precursor in the biosynthesis of paclitaxel, and semisynthesis of paclitaxel analogs (2,13,14). Recently, paclitaxel production by *Taxomyces andreanae*, an endophytic fungus, was reported. This could lead to a more economical production mode of paclitaxel (15). Doce-



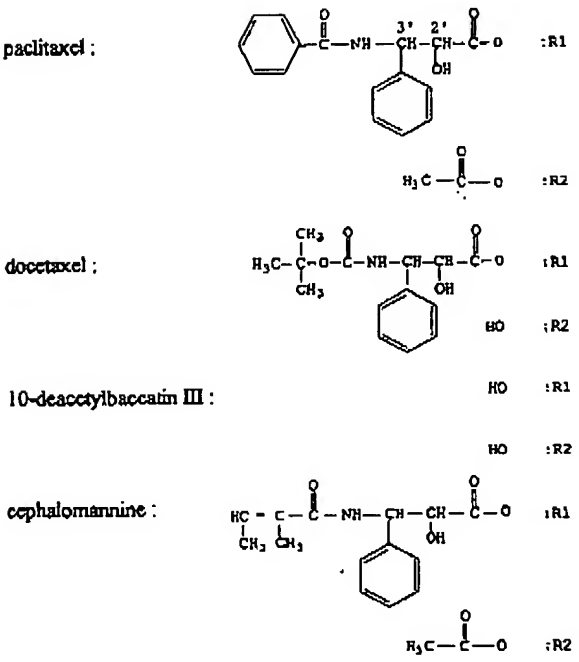


Figure 1. Structure of taxanes.

taxel (Fig. 1) is synthesized from 10-deacetylbaccatin III by esterification with a synthetically synthesized side chain ((2R,3S)-(-)-*N*-(tert-butoxycarbonyl)-3-phenylisoserine methyl ester) (16).

Chemistry

Both paclitaxel and docetaxel possess a taxane nucleus (Fig. 1), built from a diterpene carbon skeleton (17). The taxane nucleus consists of three rings. Six-membered A- and C-rings are fused at an almost perpendicular angle with an eight-membered B-ring (18). The C_{13} side chain of paclitaxel, (2'R-3'S)-*N*-benzoyl-3-phenylisoserine methylester, is esterified with the C_{13}-OH of the taxane nucleus. The naturally occurring compound has a (2'R-3'S)-configuration. Intramolecular hydrogen bonds between the estercarbonyl, 2'-OH and 3'-NH stabilize the side chain into a well-defined conformation (19). The stability of the molecule depends on whether or not epimerization takes place at C_7. Epimerization of this β-hydroxyl group takes place when the solvent (methanol) in which paclitaxel is dissolved is evaporated at relatively high temperatures under neutral (pH) conditions. A possible explanation (20) for this epimerization is a retroaldol reaction involving enolization at C_9, ring opening between C_7 and C_8, ketonization at C_7, and, subsequently, recyclization yielding either an α_1- or β_1-hydroxy configuration at C_7. Because the α_1-hydroxy group at C_7 will enable formation of a hydrogen bond with the α_1-acetoxy group at C_4, formation of this product will be facilitated. This bond appears to be very stable in paclitaxel and other analogs (21,22).

When stored in solutions, the 7-epimers change into their natural forms, apparently forming equilibrium mixtures (20). If they are stored for longer periods, ester chains are hydrolyzed (16–20,22). Paclitaxel is chemically most stable in a pH range 4–8. When it is stored in alkaline medium (pH 11.5), several degradation products are formed, which have not yet been identified (23).

Paclitaxel is poorly water-soluble. Several studies have been undertaken to increase water solubility, under the assumption that esters at C_2' are hydrolyzed in vivo, while activity is maintained (24). Prodrugs have been synthesized by esterification of ammonio or carboxylate substituents at C_2' (25). Other efforts in this regard have included the esterification of succinyl (26) or sulfonate substituents (27). The prepared compounds proved to be more water-soluble than paclitaxel, but they were less biologically active and not chemically stable. Paclitaxel shows good solubility in organic solvents (19), but these are not suitable for i.v. administration (28).

Pharmaceutical Properties

As can be anticipated, from the foregoing formulation of paclitaxel for i.v. aqueous solution was difficult because of its poor water solubility. The current formulation of paclitaxel for in vivo administration is a 6 mg/ml solution, in a solvent consisting of 50% polyoxyethylated castor oil (Cremophor EL®) and 50% dehydrated alcohol, USP. When administered as an infusion, the formulation is diluted in either 5% dextrose or 0.9% sodium chloride. Paclitaxel may occasionally crystallize in these aqueous

solutions. Thus in-line filtration is used in administration of the drug for elimination of potential microcrystals. The carrier solution of paclitaxel, Cremophor EL®, is implicated as a potential cause of anaphylactic reactions in humans. The compound has been proven to cause hypersensitivity reactions in dogs (29). Other solvents have been tested with the objective of diminishing the risk of hypersensitivity reactions. Polyethylene glycols negatively influenced the in vitro activity of paclitaxel. At present, therefore, Cremophor EL® is the only acceptable carrier (30,31).

The stability of paclitaxel in i.v. fluids was studied in various containers (23). Because relatively large amounts of di(2-ethyl-hexyl)phtalate leach from polyvinylchloride infusion bags, paclitaxel formulations should be stored in glass or polyolefin containers. Infusion through a polyethylene-lined i.v. set is also mandatory.

Dilutions containing paclitaxel for administration (concentration: 0.3–1.2 mg/ml) are physically and chemically stable for up to 24 hr (23).

In contrast to the paclitaxel formulation, docetaxel, supplied by Rhone-Poulenc Rorer laboratories, is delivered in vials containing 15 mg/ml in 50% polysorbate 80 (Tween 80). When administered as infusion, the formulation is diluted in 5% dextrose solution to a maximum concentration of 0.3 mg/ml. This procedure ensures that the polysorbate 80 concentration will not exceed 1%. Higher concentrations were shown to lead to hemolysis in dogs (32).

Bioanalysis

For the analysis of paclitaxel in biological matrices, only HPLC methods have been reported. An overview is listed in Table 1. An attractive method was published by Rizzo et al. (33). These investigators utilized a HPLC system consisting of a C_8 Hypersil 5 μm (150*4.6 mm) column, with a methanol-acetate buffer (pH 4.5, 0.02 M) as the mobile phase (65:35 v/v). The detection wavelength was set at 227 nm, with 6 min for total analysis. Paclitaxel showed a retention time of 3.5 min. Sample pretreatment involved a liquid-liquid extraction with *t*-butylmethylether followed by a solid-phase extraction with a C_{18} column. Paclitaxel and metabolites were eluted from the column with 70% acetonitrile in water. This mixture was azeotropic and evaporated at room temperature, minimizing the formation of the 7-epimer. The recovery of this method was 88% with a detection limit of 85 ng/ml. The investigators reported one unidentified peak in the HPLC chromatograms of extracts of plasma from a cancer patient. Detection of more (polar) metabolites, which elute before paclitaxel, is difficult with this system due to interferences with endogenous compounds. Recently a highly sensitive HPLC method with a solid-phase extraction as the pretreatment procedure has been developed (34,35). Paclitaxel concentrations as low as 0.012 μM (6 ng/ml) and metabolites can be detected with this system. An APEX octyl analytical HPLC column (4.6 × 150 mm; particle size 5 μm) was used. The mobile phase consisted of acetonitrile-methanol-0.02 M ammonium acetate buffer pH 5.0 (4:1:5, v/v/v). Solid-phase extraction was performed with Bond Elut Cyano Columns and UV detection was performed at 227 nm. With this assay, metabolic products of paclitaxel could be systematically detected in human plasma (35).

A possible explanation for the absence of metabolites in previous studies might be the use of a liquid-liquid extraction method as sample pretreatment. Liquid-liquid extraction, utilized by most investigators in the sample pretreatment for the bioanalysis of paclitaxel, is probably not suitable for the analysis of more polar metabolites.

For the determination of docetaxel concentrations, reversed HPLC methods with solid-phase extraction have been reported (Table 1) (36,37). No metabolites could be demonstrated in these studies.

PHARMACOLOGY

Mechanism of Action

In 1979, paclitaxel's unique mechanism of action was discovered by the Horwitz laboratory at Albert Einstein College of Medicine (3,38). It was demonstrated that paclitaxel binds preferentially to microtubules rather than to tubulin dimers. It was also observed that paclitaxel-treated cells generated large amounts of cytoplasmic microtubules (3). Microtubules are important structural elements in all eukaryotic cells and are essential for mitosis, intracellular transport, maintenance of cell shape, cellular motility, and attachment. They also play a key role in modulating interactions with cell-surface receptors and the transmembrane signals generated by these interactions. Microtubules are formed through polymerization of two different proteins, α_1- and β_1-tubulin, under the influence of cofactors such as GTP and microtubule-associated proteins (MAPs) (39). Microtubules are usually in a state of dynamic equilibrium with the tubulin dimers. Paclitaxel and docetaxel are strong inhibitors of eukaryotic cell replication, blocking cells in the G2 mitotic phase of the cell cycle. They

Table I

Analysis of Paclitaxel and Docetaxel in Biological Matrices

Sample pretreatment	Column (dimensions in mm)	Eluent	Flow rate (ml/min)	Detection limit (ng/ml)	IS	T_R (min)	Metabolites	Ref.
			Paclitaxel					
L-L followed by SPE	MOS-hypersil C_8 (150*4.6)	Methanol-acetate buffer (pH 4,5;0.02 M) 65:35 v/v	2.00	85	No	3.5	Yes	33
PP	Partisil 10 ODS (250*4.6)	Acetonitrile-water 50:50 linear gradient 10 min 85:15	1.50	n.r.	No	5.2	n.r.	47
PP followed by SPE	Varian C_{18} MCH-10 (300*4)	Methanol-phosphoric acid (1 mM) 75:25	0.75	25	No	n.r.	n.r.	49
Centrifugation dilution	Waters C_{18}	Acetonitrile-perchloric acid (1 mM) 58:42	1.00	50	No	n.r.	n.r.	49
L-L	Waters C_{18} RadialPak (100*8)	Acetonitrile-water 35:65 exponential gradient 20 min 100:0	2.50	25	N-Cyclohexyl benzamide	19.5	No	50
SPE	Apex octyl (150*4.6)	Acetonitrile-methanol 0.02 M ammonium-acetate buffer 4:1:5 v/v/v	1.00	10	No	10	Yes	34/35
SPE	ODS-hypersil C_{18} (100*4.6)	Acetonitrile-water 45:55	1.00	11	Cephalomannine	9.6	No	169
			Docetaxel					
SPE	Spherosil C_{18} (250*4.6)	Methanol-0,3% orthophosphoric acid 67.5:32.5 v.v	1.00	10	Paclitaxel	11	No	36
SPE	Spherisorb S5 ODS2 (250*4.6)	Methanol-0,1 orthophosphoric acid 67:33	1.00	15	No	n.r.	No	137
SPE	Spherisorb C_{18} ODS (250*4.6)	Methanol-0,3% orthophosphoric acid 70:30 v/v	1.00	15	Paclitaxel	9.5	No	37

L-L, liquid-liquid extraction; PP, protein precipitation; SPE, solid-phase extraction; IS, internal standard; T_R, retention time; n.r., not reported.

promote microtubule assembly by shifting the dynamic equilibrium toward microtubule assembly and stabilize microtubules, even in the absence of GTP or MAPs. Older, well-known antimicrotubule agents like the vinca alkaloids induce depolymerization of microtubules. In addition, microtubules treated with these two compounds were found to resist disassembly under conditions (4°C or $CaCl_2$) that would cause depolymerization of microtubules in their absence (7,40). Inhibition of post-translational tyrosinolation of tubulin α chain was demonstrated in rat leukocytes and human neutrophils (41).

Structure-Activity Relationships

Several derivatives of paclitaxel have been tested for their cytotoxic properties and their ability to interfere with microtubule assembly (24–28,42).

Manipulations on the C_7-moiety in the taxane nucleus did not alter activity or solubility very much. However, a decrease of the effect on microtubule assembly was measured when substituents were branched at C_7.

The presence of the side chain at C_{13} is a prerequisite for both cytotoxic activity and the effects on microtubule assembly. The sterical configuration of the side chain, (2′R-3′S) in paclitaxel, has also been shown to be of importance for activity. Comparison of the activity of the 2′S-3′R) compound and paclitaxel showed that paclitaxel was approximately four times more active (42).

The hydroxyl group at C_2′ is necessary for microtubule interaction and the effects on microtubule assembly and has been shown to possess the highest activity when in an R-configuration. Increased water solubility was found when acyl or amino acid substituents were attached at

this binding place (43). When the C_2'-OH is masked, hydrolysis of the substituents at their place of action is needed for activity. When this process is not complete (due to stability of the prodrug), little or no activity is seen. On the basis of these findings, several prodrugs have been synthesized (25–28).

Replacement of the phenyl group at C_3' by smaller groups (e.g., methyl) results in a major loss of activity. Other hydrophobic substituents do not influence the biological activity. *N*-Amide substituents show higher activity than amino substituents.

The taxane nucleus is important for binding on the microtubule. The bond is stabilized by the side chain and this mechanism creates the specificity (42).

The binding site for paclitaxel was not found on single tubulin dimers. Probably the paclitaxel binding site is formed when two tubulin dimers are connected, thereby inducing a conformational change (39). Direct photoaffinity labeling of tubulin with radiolabeled [^{3}H] taxol shows that taxol binds covalently to the β-subunit of tubulin (44).

When paclitaxel undergoes deacetylation at C_{10} and replacement of the benzamide phenyl group by $NHCOOC(CH_3)_3$ at C_3', yielding docetaxel, the antitumor action is retained (7). Coupling of chloride at the phenyl group on C_2' or C_3' did not alter the activity in a tubulin assembly assay (45).

Pharmacokinetics

Pharmacokinetic parameters of paclitaxel at the recommended doses for phase II trials are summarized in Table 2. In early phase I studies, pharmacokinetic disposition of paclitaxel has been described by a simple two-compartment model, whereby the area under the plasma concentration versus time curve (AUC) is linearly related to dosage (46–51). These biexponential kinetic characteristics provide two half-lives after termination of the infusion. The first half-life $t_{1/2\alpha}$ is about 0.4 hr and $t_{1/2\beta}$ is about 6 hr.

The systemic clearance, calculated as dose/AUC, is approximately 8 L/hr/m^2 (dose: 175 mg/m^2) with a renal clearance, found in most studies, of about 7 ml/min/m^2 (urinary excretion of unchanged drug 2–10% of the administered dose) (47). The apparent volume of distribution is large (range 40–657 L/m^2). Equilibrium dialysis studies (47) and ultracentrifugion techniques (50) have indicated a serum protein binding of 93–98% over a wide range of concentrations. These data indicate that renal clearance is rather insignificant and that metabolism, biliary excretion, and/or extensive tissue binding is probably responsible for the total body clearance of paclitaxel.

In later studies indications for nonlinear pharmacokinetics have been found (35,52). With an increasing dosage given by 3-hr infusion there is an unproportional increase in maximally reached plasma concentration (C_{max}) and area under the curve (AUC). Results obtained with the use of more sensitive HPLC assays with a low threshold of quantitation (0.012 μM) have suggested the existence of a triexponential decay. An initial rapid decline represents significant elimination of the drug from the circulation and tissue distribution. The prolonged terminal phase may represent a slow reflux of paclitaxel into the circulation (35). Changes in dose or in infusion schedules have resulted in different pharmacokinetic parameters (Table 2) (35,52–56).

Paclitaxel has excellent pharmacological properties for intraperitoneal (i.p.) administration. In patients with ovarian cancer, paclitaxel dosages of 100 mg/m^2 could be safely delivered in the peritoneal cavity with minimal systemic and local toxicity (57). The i.p. concentrations were several orders of magnitude higher than the minimal drug concentrations (>0.1 μM) that are required to induce microtubule bundling and other pertinent cytotoxic effects in vitro. Mean peak plasma concentrations correlated only roughly with the administered dose, which suggests wide interindividual variability in absorption and significant anatomical differences. However, i.p. concentrations, even 24–48 hr after drug administration, were several orders of magnitude higher than the maximal plasma levels that have been achieved in patients who were treated i.v. with maximal tolerated doses of paclitaxel administrated during a 24-hr period.

The i.p. clearance of paclitaxel is low (with an elimination half-life of about 75 hr), which indicates that biologically relevant concentrations can be attained for a prolonged period. Paclitaxel may have the lowest i.p. clearance of any known antineoplastic agent.

These pharmacological characteristics may be critical in deriving maximal benefit from treatment of slowly growing neoplasms with cell-cycle-specific agents such as paclitaxel and other antimicrotubule agents in which cytotoxic activity is related to the duration of exposure.

Plasma pharmacokinetics of docetaxel were best described by a biexponential model for doses below 70 mg/m^2 and a triexponential model for doses above 85 mg/m^2 (Table 3). The terminal phase probably reflects redistribution from peripheral tissues. Urinary excretion of docetaxel is low: 2–6%. In a 5-day schedule, docetaxel could only be detected for 7 hr after the end of infusion. Peak plasma concentrations increased linearly with AUC

Table 2

Mean Pharmacokinetic Data of Single-Dose Paclitaxel

Ref.	No. of patients	Dosage in mg/m^2 (infusion time in hr)	AUC (mg/L.hr)	V_d (L/m^2)	CL_T (L/hr/m^2)	$t_{1/2}$ (elimination) (hr)
49	4	15–30 (1)	24	80	53	1.5
	4	30–40 (6)	53	82	54	1.4
48	2	175 (6)	8.4	40	20	2.5
	3	225 (6)	22	47	11	5.6
	2	250 (6)	10	60	19	5.1
	2	275 (6)	34.6	46	8	7.6
46	3	200 (24)	9.7	65	21	2.9
	3	250 (24)	12.7	110	20	3
	3	275 (24)	12.4	182	23.5	3.9
47	4	175 (6)	22.5	64	8	8.6
	2	200 (6)	23.4	53	8.6	7.1
	3	230 (6)	25	66	9.6	8.9
	3	275 (6)	48.5	55	6	8.6
52	4	135 (3)	9.22	n.r.	12.55	n.r
	3	175 (3)	15.8	n.r.	9.65	n.r
	8	250 (3)	31.85	n.r.	6.83	n.r
	3	300 (3)	40.6	n.r.	6.49	n.r
53	3	135 (24)	9.5	164	14.76	17.1
	3	180 (24)	10.6	169	17.28	13.7
55	3	100 (24)	9.28	193	11.22	24.9
	3	150 (24)	10.52	188	14.88	22.0
	3	200 (24)	14.31	149	14.16	12.9
35	7	135 (3)	8	98	15.11	14.4
	2	135 (24)	6.24	657	18.62	49.7
	5	175 (3)	14.35	99	10.84	18.7
	4	175 (24)	7.94	269	20.06	19.6
169	48	250 (24)	17.3	n.r.	15.4	n.r.

AUC, area under the curve; V_d, distribution volume; CL_T, systemic clearance; $t_{1/2}$, terminal half-life; n.r., not reported.

and within individual patients peak plasma concentrations were constant over the 5 days. These data indicate that there is no drug accumulation. The interpatient variability is considerable (58). An excretion balance of docetaxel was investigated with ^{14}C-docetaxel (59). Blood, plasma, plasma ultrafiltrate, saliva, feces, and urine were collected. About 80% of total radioactivity was excreted by feces during the first 48 hr. Only 5% of the total radioactivity was excreted in urine. Saliva contained very small amounts of radioactivity (59); however, no docetaxel could be identified in saliva (32,59). No ^{14}C-CO_2 was found during a breath test (59).

Metabolism

The principal mechanisms in systemic clearance have not yet been identified. Until 1992 paclitaxel metabolites had not been identified in human plasma (60). This is most likely due to the fact that highly sensitive and selective assays for determination of the putative paclitaxel metabolites were lacking. Recently, Monsarrat et al. found nine metabolites in rat bile, using HPLC analysis (61). Forty percent of the injected dose was eliminated in bile over the first 24 hr. Three major compounds were isolated and characterized structurally. One component was baccatin III, present in the lowest concentration.

The other two compounds were formed by hydroxylation at the para-position of the phenyl-moiety at C_3' and at the meta-position of the benzoate group at C_2. In vitro experiments showed that these metabolites possessed a decreased cytotoxicity, while baccatin III is not active at all. Data on the analysis of paclitaxel metabolites in bile of one patient have been reported recently; baccatin III

Table 3

Mean Pharmacokinetic Data of Single-Dose Docetaxel

Ref.	No. of patients	Dosage in mg/m^2 (infusion time in hr)	AUC (mg/L.hr)	V_d (L/m^2)	CL_T (L/hr/m^2)	$t_{1/2}$ (elimination) (hr)
37	6	100 (6)	6.8	98.7	16	12.4
	8	100 (2)	5.2	81.6	20	11.4
137	5	90 (24)	7.8	36.2	19.5	n.r.
58	6	16 (1)	0.5	73	33	3.6
125	6	85 (2)	4.1	72	22.6	13.6
	4	100 (2)	5.9	95	17	18.5
	4	115 (2)	5.2	53	22.2	9.6

AUC, area under the curve; V_d, distribution volume; CL_T, systemic clearance; $t_{1/2}$, terminal half-life; n.r., not reported.

was not found (62). Apart from a hydroxylated metabolite, which was also present in rat bile, 6-hydroxytaxol was found to be a major metabolite. By using a highly sensitive HPLC assay, we were also able to detect metabolites in plasma of patients treated with paclitaxel (35). The data on paclitaxel metabolism are scanty and more studies are needed to reveal the structures of the metabolic products found so far and their clinical relevance. A common major metabolite, RPR 104952, was found in plasma, bile, and feces of mice and dogs in a radioactivity study with ^{14}C-docetaxel. No additional structural information was given (63).

To date, no docetaxel metabolites in humans have been reported, as far as we know.

Drug-Drug Interactions

Biliary excretion of paclitaxel and metabolites (hydroxylation probably involves the P-450 cytochrome C oxidase system) may account for a major portion of the drug disposition. H_2-receptor blockers, used as premedication for hypersensitivity reactions during paclitaxel therapy, have a variable effect on P-450 functions, which may theoretically influence the pharmacological profile and, therefore, the toxicity and antitumor effect of the drug. In one study 70 patients received multiple cycles of a 24-hr infusion of paclitaxel. During one cycle, "high dose" cimetidine (100 mg/m^2) was concomitantly (for 24 hr) added to investigate the influence on paclitaxel metabolism. Each patient served as his own control. No differences in steady-state levels of paclitaxel were observed, which rules out substantial contributions from paclitaxel metabolic pathways sensitive to cimetidine (64,65).

The influences of two different H_2-receptor blockers, famotidine and cimetidine, on paclitaxel kinetics were compared in a randomized study (66). The steady-state concentration (C_{ss}) of paclitaxel was significant higher after famotidine administration with a significantly lower clearance; no differences in toxicity were observed.

Ketoconazole, a potent inhibitor of the P450IIIA4 system, decreased the formation in vitro of one of the two observed paclitaxel metabolites in a preparation of human liver slices and microsomes (67). Concomitant administration of ketoconazole in vivo produced a moderate increase in paclitaxel levels, but a dramatic decrease in biliary metabolite excretion (68).

Fluconazole had a similar effect to that of ketoconazole, but is at least 10 times less potent (69).

In vitro cytotoxicity studies showed sequence dependence of paclitaxel and cisplatin. IN L1210 leukemia cell lines a maximal cytotoxicity was seen when paclitaxel preceded cisplatin (70). In human ovarian carcinoma cell lines, a synergism was observed when 19-hr taxol exposure was followed by 1 hr of concurrent paclitaxel and cisplatin exposure. Antagonistic action was seen when cisplatin preceded paclitaxel (71). Another study, which used fresh ovarian cancer specimens, found only a subadditive inhibition when paclitaxel was added prior to, at the same time, or within 6 hr of cisplatin exposure. An additive effect was observed only when cisplatin was administered 24–48 hr prior to paclitaxel (72). Paclitaxel and cisplatin act synergistically in human ovarian cancer A2780/CP70 cells, and this synergism is maximal with a 24-hr interval between paclitaxel and cisplatin administration (73). Also, inhibition of DNA-adduct repair was maximal with this regimen (74).

In a sequence finding study of cisplatin and paclitaxel in patients, a more profound neutropenia was observed when cisplatin preceded paclitaxel (75). Pharmacokinetic monitoring revealed that this difference was probably due to 25% lower paclitaxel clearance rates when cisplatin

preceded paclitaxel. The paclitaxel clearance rate was 321 ± 44 ml/min and 405 ± 65 ml/min for the alternate sequence.

The combination of paclitaxel and carboplatin in a clinical study showed cumulative myelosuppression (76). There was no significant increase in AUC of carboplatin. No pharmacological data of paclitaxel in this combination therapy are available at the moment. In several preclinical studies activity and toxicity were tested for combinations of drugs with paclitaxel. There was no therapeutic advantage of the addition of 5-fluorouracil. Less than additive cytotoxicity was seen for the combination paclitaxel with doxorubicin or etoposide in three human cell lines (MCF7, A549, OVG1) (77).

Concomitant administration of the antiepileptic drug phenytoin increased paclitaxel cytotoxicity in both sensitive and multidrug-resistant (MDR) cells (78).

Tiazofurin (an antimetabolite) acts synergistically with taxol in several cell lines, e.g., OVCAR-5, PANC-1, H-125, and 3924A (79).

Several drug combinations with docetaxel were evaluated in in vivo studies for drug synergism. Docetaxel showed marked synergism with cyclophosphamide, etoposide, and 5-fluorouracil against transplantable tumors in mice (80). In the SKBR-3 human breast cancer cell line, a synergism was found whenever edetrexate was followed by administration of docetaxel or paclitaxel. In the reverse order, only an additive effect was seen for docetaxel and an antagonistic effect for paclitaxel (81).

1,25-Dihydroxyvitamin D_3 interacted synergistically with paclitaxel in vitro and in vivo with MCF-7 breast cancer cell lines (82).

PRECLINICAL ACTIVITY

Toxicology

The toxicology of paclitaxel was established in NCI preclinical studies in CD2F1 mice, Sprague-Dawley rats, and beagle dogs (83). In lethality studies the animals were exposed with a single dose for 1 day or for 5 consecutive days. These studies provided LD_{10}, LD_{50}, and LD_{90} (dose lethal to 10%, 50%, and 90%) values of 138, 206, and 307 mg/m^2, respectively, in rats for the single dose. If the administration of paclitaxel was spread over 5 days, values of LD_{10}, LD_{50}, and LD_{90}, decreased to one-fourth (36, 51, and 74 mg/m^2, respectively). Toxic effects of paclitaxel were found in tissues with a high frequency of cell turnover, such as hematopoietic, lymphatic, gastrointestinal, and reproductive tissues; this was found in all three species. In beagle dogs, myelosuppression occurred, which was cumulative and reversible between 45 and 180 mg/m^2 in a single-dose schedule. On a 5-daily dose schedule, the dose for myelosuppression was 15–30 mg/m^2. Dogs receiving this schedule showed severe gastrointestinal effects such as weight loss, diarrhea, emesis, adipsia, and mucosal ulcerations. Diffuse inflammation and congestion of both the small and the large intestines occurred in dogs at lethal doses. Depression of the central nervous system, namely lethargy, coma, and ataxia, was also observed in dogs. All species showed a dose-related lymphoid depletion.

In rats and mice, testicular lesions were observed. These lesions were characterized by necrosis of developing spermatocytes, giant cell formation in the seminiferous tubules, and oligospermia (83).

In vitro tests have shown that paclitaxel causes the formation of abnormal bundles of microtubules throughout the cytoplasm, leading to deregulation of normal cell functions, such as mitosis, cell proliferation, neurite initiation, and neurite branching (84–89). Direct injection of paclitaxel in rat sciatic nerve showed a sustained and local toxic effect, leading to microtubule-related abnormalities in Schwann cells and axons (90–92). The effect of paclitaxel on Schwann cells correlated with changes in myelinization and the development of the nodes of Ranvier (93).

The effects of paclitaxel on neurons were mostly long-lasting but reversible. In one study, it was shown that after 3 months the paclitaxel-induced microtubule abnormalities have decreased (94).

Examination of ^{3}H-paclitaxel distribution in adult Spraque-Dawley rats showed no distribution of the radioactivity in the nervous system (limit of detection < 20 nM), with only a small amount detected in cerebrospinal fluid (CSF). In this study, high levels of radioactivity were observed in liver parenchyma, spleen, heart, lung, and muscles. Extreme high concentrations were seen in the portal triad, glomerulla, renal medulla, and choroid plexus (95).

Preclinical toxicity studies showed only minor effects on nerve, hepatic, cardiovascular, and renal tissues, with no postmortem evidence of organ damage (83). Whole-body autoradiography with radioactive-labeled docetaxel in mice and dogs showed rapid tissue uptake, e.g., in liver, bile, intestine, stomach, spleen, myocardium, bone marrow, pancreas, and salivary glands, while no uptake was seen in the central nervous system (96).

Antitumor Activity

Paclitaxel was shown to be cytotoxic in several cell culture and tumor systems. Wani et al. (2) reported in 1971, during purification of stem bark concentrate of the Western yew, *T. brevifolia*, that paclitaxel is cytotoxic in the 9KB-assay. Paclitaxel also showed high activity in L-1210, P-388, and P-1534 leukemias and in the Walker-256 carcinosarcoma model. Less pure fractions containing paclitaxel were reported to be active in sarcoma 180 and Lewis lung tumors (2).

High antineoplastic activity against murine B16 melanoma was noted in preliminary tests of the NCI (83). When paclitaxel was tested against human cultured prostate cancer cells, paclitaxel also proved to be cytotoxic (97). In addition to these reported activities, the effects of paclitaxel on xenografts of human tumors have also been studied. Significant activity was noted against the MX-1 mammary tumour (83), LX-1 lung tumors, CX-1 colon tumor, bronchial carcinoma, and primary tumors of the endometrium, ovary, and brain (83,98,99).

Despite the wide area of responses, paclitaxel was inactive in $CD8F_1$ mammary carcinoma, colon 38 carcinoma, Lewis lung carcinoma, and heterotransplanted pancreatic carcinomas (83,100).

Comparison between docetaxel and paclitaxel regarding cytotoxicity against J-774.2 and P-388 cell lines reveals that docetaxel is 2.5 times more potent in inhibiting replication than paclitaxel. The median effective dose (ED_{50}) for docetaxel was 5–6 times lower than that for paclitaxel in the MDR cell line J7.T1-50 (7).

Docetaxel also showed cytotoxic activity against several murine tumors. The compound exhibited cytotoxic activity against B16 melanoma, pancreatic ductal adenocarcinoma P03, and colon adenocarcinoma C38 and C51. No effect was noted against colon carcinoma C26 (101). Moderate effect was seen against Lewis lung carcinoma.

Responses against human xenografts have also been reported, with long-term tumor-free survivors, for the MX-1 mammary carcinoma and the OVCAR-3 carcinoma.

CLINICAL DEVELOPMENT

Toxicity

Hypersensitivity Reactions

During early clinical studies of paclitaxel, the occurrence of hypersensitivity reactions was a major concern. Most of the patients who experienced hypersensitivity had definite manifestations of type I hypersensitivity reactions, including hypotension, dyspnea with bronchospasm, and urticaria, which appeared to be mediated by the release of histamine. It is still unclear whether paclitaxel itself or its Chremophor EL®/alcohol vehicle induces those reactions by direct release of histamines as was seen in dogs (29). It also seemed as if the incidence of the hypersensitivity reactions was higher with infusion of short durations. Because of these clinical observations, protocols were modified to give paclitaxel as 24-hr infusions with the addition of prophylactic antiallergic premedications consisting of steroids and H1 and H2 antihistamines (30).

A large randomized study with a four-arm factorial design was started to evaluate the safety of a short-term infusion (3 hr) with extensive premedication mentioned above. Preliminary results from this European-Canadian study, which entered a total of 407 patients, include 286 evaluable patients with a total of 1017 courses for hypersensitivity reactions. Hypersensitivity reactions were observed in 20% (203 of 1017) of total administered taxol courses: 21% in the 24-hr infusion arm (122 of 568 cycles) and 18% in the 3-hr infusion arm (81 of 449 cycles). Significant hypersensitivity reactions were observed in only 0.4% of the treatment courses (102).

Hypersensitivity reactions from docetaxel, described in phase I studies, were less severe and less frequent in comparison with those observed with paclitaxel (32). Only 10% of the treated patients, without antiallergic prophylaxis, experienced hypersensitivity reactions such as transient rash and/or pruritus, several hours after the end of the infusion. In phase II trials evaluation of hypersensitivity reaction data by EORTC-ECTG indicated that these reactions were more frequent and more serious than initially had been reported (103); 83 reactions out of 552 courses (15%) occurred, of which 2% were severe reactions. The hypersensitivity reactions emerged within a few minutes after the start of infusion and resolved in nearly all cases within 24 hr. It should be noted that the phase II trials used for this evaluation were started without any premedication. The hypersensitivity reactions that occurred necessitated the addition of antihistamines and steroids subsequently. In contrast to paclitaxel, most reactions occurred in the second cycle.

Hematological Toxicity

Paclitaxel produces marked alterations in human neutrophil functions and morphology under both stimulated contiditions (*N*-phenyl-methionyl-leucyl-phenylalanine

or endoxine-activated serum) and basal conditions. Chemotaxis was inhibited for more than 60% with paclitaxel concentrations of 0.1 μM and decreased phagocytosis of *Staphylococcus aureus* by 10 μM paclitaxel (41).

In clinical studies, without G-CSF support, neutropenia is the principal dose-limiting toxicity (104–108). The fall in granulocyte count usually reaches the nadir during the second week (day 7–10) following therapy and reverses within 1 week.

Evaluation of 393 patients from a large randomized study in platinum-pretreated ovarian cancer patients showed clearly that neutropenic fever was infusion schedule dependent: 12% neutropenic fever during the 24-hr infusion schedule versus 0% during the 3-hr infusion schedule (102). There is little evidence that neutropenia is cumulative, and neutrophil count nadirs have generally remained constant during successive courses in high-dose paclitaxel (250 mg/m^2) and G-CSF (109).

Neutropenia and thrombopenia were the dose-limiting toxicities in a phase I study in which a combination therapy of paclitaxel (135 mg/m^2; 24-hr infusion), followed by carboplatin (AUC = 10 mg.min/ml, predicted with Calvert formula), was administered (76). The recommended AUC for carboplatin was 7.5 mg.min/ml. A striking feature of this study was the unusually high AUC for carboplatin. In most single-agent studies of carboplatin a target AUC of 7 mg.min/ml and AUC of 5 mg./min/ml for combination therapies is pursued. There was a significant difference between the target AUC (7.5 mg./min/ml) and the observed AUC (6 mg.min/ml). Myelosuppression increased with multiple cycles.

In a sequence-finding study of cisplatin in combination with paclitaxel, lower white blood cell count (WBC) and absolute neutrophil count (ANC) nadirs were reported when cisplatin preceded paclitaxel. However, no effect was seen on the duration of the nadir (75). In a sequence-finding study of paclitaxel in combination with cyclophosphamide, preliminary results show no significant difference between the two sequences (110).

Docetaxel shows the same dose-limiting profile as paclitaxel, including dose-dependent, reversible, noncumulative leukoneutropenia (32). For doses above 55 mg/m^2 in 1-hr infusion, grade 4 neutropenia is prominent for docetaxel. Neutropenia occurred between the fifth and the eighth day after docetaxel infusion with a median duration of 7 days (range 3–14). Anemia occurs more frequently with increasing courses, but rarely outside the range of grade I toxicity (111). Anemia is mostly observed after the first or second course. The major clinical risk factor for the anemia appears to be the extent of prior chemotherapy and/or irradiation. Thrombocytopenia is rare.

Neurotoxicity

Peripheral neurotoxicity has frequently been observed during the early development of paclitaxel. Phase I studies, which used infusion durations of 6- and 24-hr infusions, showed that these reactions occurred rarely at doses below 170 mg/m^2 (46,47,51,107). In later studies that used high dosages of paclitaxel (≥250 mg/m^2) with G-CSF support, neurotoxicity became dose-limiting (112,113). Neuromuscular toxicity is dose-limiting in the combination therapy of paclitaxel with cisplatin and G-CSF (114). The incidence and severity of neurotoxicity are dose-related and, after cessation of therapy, partly or completely reversible (115,116).

Recently Rowinsky et al. categorized the neurotoxic manifestations of paclitaxel into five groups (a) sensory neuropathy, (b) motor neuropathy, (c) autonomic neuropathy, (d) myopathy or myopathic effects, and (e) central nervous system effects (117).

Paclitaxel-related peripheral neurotoxicity has been principally characterized by neurosensory manifestations. The most common symptoms are numbness and paresthesias in a glove-and-stocking distribution. Neurotoxicity is dose-related and cumulative and progressively worsens after multiple courses (115,117). Electrophysiological findings in several symptomatic patients included decreased nerve conduction velocities in sensory nerves, with relative sparing of motor nerves (115,118, 119).

Significant elevations in vibratory and thermal thresholds have also been detected. The electrophysiological data support both axonal degeneration and demyelinization as mechanisms for paclitaxel-induced neurotoxicity.

Sensory symptoms usually improve or resolve within several months after discontinuation of paclitaxel therapy (46,47,51,106).

Motor neuropathy is characterized by mild weakness of the extensor hallucis longus weakness and diminished grip strength with reduction in peroneal nerve–evoked amplitude of the extensor digitorum brevis.

Paralytic ileus and symptomatic orthostatic hypotension are autonomic neuropathy manifestations of paclitaxel (46,47,75).

Muscular weakness is frequently reported when patients receive higher doses of paclitaxel or when paclitaxel is combined with either cisplatin or carboplatin (114,115,119,120). Patients complained about weakness of the upper extremities and difficulty in climbing stairs

and rising from a sitting position. EMG studies demonstrate myopathic motor unit potentials in the proximal muscles and prolonged H-reflexes (114,118,119). Biopsy of the muscles showed, with acid phosphatase staining accumulation of lysosomes, suggesting nonspecific toxic myopathy (114,118). Neuroencephalopathy has been reported as a possible adverse event in one patient (121). Shortly after administration of paclitaxel, sensory and motor impairment of the lower limbs occurred with radiation of pain to the upper limbs, breast, and face in combination with visual impairment and behavioral disorder. All signs resolved within 38 days. Manifestation of grand mal seizures was documented during early trials (48,104), although there are no indications that paclitaxel can pass the blood-brain barrier (51).

Comparing nonrandomized phase II studies of paclitaxel and docetaxel, neurotoxicity seems less severe during docetaxel ($\leq$110 mg/m^2) administration compared to high-dose paclitaxel with G-CSF support (paclitaxel $\geq$ 250 mg/m^2). Analysis of the toxicity data by EORTC-ECTG of phase II studies that enrolled 427 patients with docetaxel showed that neuropathy > grade I is rare (111). Until now no studies were published where neurotoxicity is dose-limited, although dose escalation with G-CSF has not been published.

Docetaxel neurotoxicity consisting of mild paresthesias and abolition of the tendon reflexes appeared above doses of 85 mg/m^2 (122). Moderate or severe reactions occurred more in patients with pretreatment with platinum compounds or vinca alkaloids. In a 5-day schedule neither neurotoxicity nor cardiotoxicity was observed (58). Neurological nerve-conducting velocity and quantitative small nerve fiber sensory testing showed no abnormalities.

Cardiotoxicity

Paclitaxel can cause asymptomatic atrioventricular conduction abnormalities in association with sinus bradycardia (heart rates range from 30 to 50 bpm) in patients who received paclitaxel as a single agent or in combination with cisplatin (75,123,124).

Ventricular tachycardia associated with ventricular ectopy has also occurred on rare occasions in patients who were treated with the combination paclitaxel and cisplatin (75). One study reported asymptomatic sinus bradycardia during one or more courses in 29% (13/45) of ovarian cancer patients without being at cardiac risk (104). In 2 patients, however, delay of atrioventricular conduction (>grade 1) occurred, namely Mobitz type I, atrioventricular block with 2:1 conduction, and complete heart block (123).

One patient with preexisting hypertension and hypercholesterolemia treated with cisplatin and paclitaxel died of myocardial infarction during paclitaxel infusion. Left bundle branch block occurred in 1 patient during paclitaxel infusion and resolved after discontinuation of paclitaxel. Artrial fibrillation has been noted in several patients after paclitaxel administration, responding to digoxin or digoxin in combination with verapamil and esmolol. One patient suffered from a myocardial infarction 2 days after paclitaxel administration and another had mild congestive heart failure with orthopnea and reduction of left ventricular ejection fraction from 51% to 38%.

Bradycardia (<60 bpm) was found in 10 of 15 patients during the first cycle; one patient had a transient, asymptomatic, self-limited episode of Mobitz type I (Wenckebach) second degree heart block, 19 hr after paclitaxel administration. A second patient had an episode of dizziness, nausea, and hypotension (systolic pressure 66 mmHg) occurring 6 hr after completion of the second cycle; no ECG abnormalities were observed (123). Investigators from the National Cancer Institute concluded that routine cardiac monitoring is not to be recommended in patients without cardiac risk, but patients with potential cardiac risk factors should be excluded from receiving paclitaxel (124).

Cardiac disturbances associated with docetaxel administrations have not been reported.

Cutaneous Toxicity

Cutaneous toxicity is a serious and frequent event (28%) seen with docetaxel administration. These cutaneous reactions, which are rare with paclitaxel, are highly variable and consist of erythema and swelling of the hands and feet, sometimes accompanied by bullous lesions, followed by dry desquamation after subsequent courses. Histological examinations showed nonspecific toxidermic cutaneous reactions or sclerodermic changes, which may be compatible with a drug eruption. The first signs of cutaneous toxicity usually occurred in the second week following the first or second infusion, often with a partial recovery within 15 days (32).

The cutaneous reactions are dose-dependent and cumulative and rarely have been seen at doses below 85 mg/m^2. A study comparing 2- and 6-hr infusion schedules shows slightly more dermatitis in the 6-hr infusion arm (4/6 versus 6/18) (37). Hypersensitivity prophylaxis did not improve or prevent the cutaneous toxicity (32,125,

126). Regular application of an ointment consisting of glycerin and chlorhexidine led to a remarkable improvement of the skin lesions to a level acceptable to the patient (127).

Edema

Another remarkable feature during docetaxel treatment is the observation of diffuse subcutaneous edema with weight gain (32). Pooled safety data of 473 patients in several phase II studies using a 1-hr infusion with a dose of 100 mg/m^2 showed an incidence of 60% of edema (111). The edema was mostly localized to lower extremities, ankle and pretibial, abdominal wall, periorbital, face, and breast. Pleural effusions are frequently reported (dose: 100 mg/m^2); they seem to be related to cumulative courses ($\geq$4) and are often reason to stop the treatment (111,125,126,128–130).

The cutaneous reactions are dose-dependent and cumulative and have not been seen at doses below 85 mg/m^2.

In a group of 35 patients 9 developed edema (25%, 95% confidence interval 12.5–43%). Comparison between patients with and without premedication who developed acute hypersensitivity reactions revealed more edema in the group without pretreatment (8/22, 36%, 95% CI 17–59%) with corticosteroids and antihistamines (1/13, 8%, 95% CI 0.2–36%). A possible explanation could be damaging of the endothelium due to inflammation, exacerbated by repeated docetaxel exposure (127). Edema and weight gain were not responsive to diuretics in most studies with the exception of that of Extra and colleagues (32). Premedication used in this study for acute hypersensitivity reactions seems to have a preventive effect on the development of edema (127).

None of these reactions occurred during paclitaxel administration. This may be due to the extensive premedication schedule.

Gastrointestinal Toxicity

Gastrointestinal toxic effects due to paclitaxel are low in incidence and usually vary in severity. They include mucositis, vomiting, and diarrhea. Mucositis was dose-limited in an early phase I study with a single "high dose" paclitaxel (>300 mg/m^2) during 24-hr administration in patients with leukemia (51). The mucositis consisted of diffuse ulcerations of the oral cavity and pharynx. Postmortem examination showed arrest in mitosis and epithelial necrosis. The mitotic arrest induced by paclitaxel seems to be transient because no abnormalities were found in patients examined 17 days after paclitaxel administration (131).

In general, severe stomatitis mostly occurred in combination with severe neutropenia (<500/mm^3) or infection during prolonged infusions (96–120 hr) (132,133). The combination therapy with low-dosage, prolonged paclitaxel infusion (125 mg/m^2, 24 hr), followed by doxorubicin (60 mg/m^2, 48 hr) (134) or concomitant administration of paclitaxel and doxorubicin over 72 hr, shows, besides severe neutropenia with fever, also grade III–IV gastrointestinal complaints consisting of severe diarrhea, abdominal pain, and typhlitis (135).

Abdominal pain is the dose-limiting toxicity of paclitaxel when administered into the peritoneal cavity at doses greater than 125 mg/m^2. The pain began 8–24 hr after instillation was begun (57).

Elevation from baseline hepatic functions [bilirubin (8%), alkaline phosphatase (23%)] and transaminase (33%) concentrations were observed in 4–17% of the patients treated in doses below 190 mg/m^2 versus 16–37% of the patients at higher doses (136). All patients treated with paclitaxel had normal baseline values. Paclitaxel is extensively metabolized by the liver; therefore, caution is warranted in patients with liver impairment.

Elevations in serum triglyceride and cholesterol levels have also been observed (106,132). Mucositis associated with docetaxel administration during short-term infusion (1–2 hr) is rare and was seen only during prolonged infusion or during short infusion for 5 consecutive days (32). Mucositis was characterized by painful oral erythema progressing to ulceration. The oral reactions started within 48 hr of completion of the docetaxel infusion and healed over 3–10 days. Prophylactic mouth washings and the anticandidal agent nystatin did not prevent this toxicity. Significant oral mucositis is uncommon with doses lower than 85 mg/m^2 when docetaxel is infused over 1–2 hr every 3 weeks.

During a 5-day schedule, grade IV granulocytopenia in combination with grade III mucositis was the main feature (doses > 10 mg/m^2/day) (58). The mean onset of mucositis was on day 10 with a mean duration of 6 days. Diarrhea occurred when the severity of oral mucositis was greatest (16 mg/m^2/day), indicating generalized mucosal injury. It is likely that coincident oral mucosal ulceration (grade III) provided the portal of entry for these infections. Less mucositis could potentially reduce bacterial entry into a neutropenic patient.

Since the greatest dose intensity has been achieved with a 1–2-hr infusion administered once every 3 weeks, phase II studies have begun with this schedule at a dose of 100 mg/m^2. This dose is expected to cause a brief

period of grade IV neutropenia, but in the absence of mucositis it is unlikely to lead to a significant number of septic episodes. Drug-related hyperbilirubinemia was reported in 1 patient treated with docetaxel 90 mg/m^2 during 24 hr. Icterus started 8 days after the first course. It occurred in association with neutropenia and sepsis, but there was no evidence of intravascular hemolysis (137).

Alopecia

Reversible total alopecia is observed in almost all patients treated with either paclitaxel or docetaxel. It appears suddenly and it is often complete, with the loss of all body hair, including axillary and pubic hair, eyelashes, and eyebrows. Generally, alopecia occurs in the third week after the first administration (32). Paclitaxel-induced alopecia is usually reversed completely 6–8 weeks after treatment.

Alopecia is dose-related and appears above 55 mg/m^2 for docetaxel and 90 mg/m^2 for paclitaxel.

Miscellaneous

Paroxystic pain syndrome, transient myalgias, and arthralgias with or without painful dysesthesia, mainly of the lower extremities, have been observed after paclitaxel administration, with symptoms occurring 2–4 days after treatment lasting 24–72 hr. Arthralgias and myalgias are usually mild and infrequent at paclitaxel doses $\leq$170 mg/m^2 and more severe (grade III using narcotics) when doses are increased above 200 mg/m^2. Treatment with low-dose oral antihistamines and prednisone (40 mg every 2–4 days) were reported to give partial or complete relief of all symptoms (112,138).

A case report described fatal pulmonary lipid-embolism in a patient with underlying pulmonary disease who received paclitaxel. The cremophor EL vehicle and concurrent use of corticosteroids were implicated (139).

Local venous toxic effects with erythema, tenderness, and discomfort along the course of the injected vein and cellulitis in areas of dermal extravasation have also been noted. Extravasation of docetaxel leads to pain and discoloration of the skin, and skin continues to be erythematous, with occasional peeling for up to 6 weeks. No necrosis or ulceration of the skin, subcutaneous tissues, or tendons has been seen so far (32). Nail changes, with brown discoloration, onycholysis, and growth arrest were observed at docetaxel doses $\geq$ 100 mg/m^2 (32).

Toxicity in Pediatrics

Neuropathy appears to be the dose-limiting toxicity of paclitaxel in pediatric oncology (140,141). Neuropathy, namely sensory or motor loss and general seizures, is also mentioned and is dose-related. Grade IV neutropenia did not occur but several episodes of neutropenic fever occurred at doses higher than 240 mg/m^2.

Mucositis, diarrhea, pancreatitis, hemorrhagic cystitis and hypertension have been observed in doses above 240 mg/m^2. No cardiac toxicity was seen in these studies. As far as we know, docetaxel has not been tested yet in childhood cancers.

Antitumor Activity

The clinical activity of paclitaxel has been established in several phase II studies, which are outlined in Table 4.

Paclitaxel shows activity in metastastatic ovarian, breast, non-small cell lung, small cell lung cancer (142), esophageal cancer (143), and head and neck cancer (144). Limited efficacy was seen in tumors of the upper gastrointestinal tract (145) and malignant melanoma (146). No activity has been observed in patients with metastatic renal cell cancer (147), colon cancer, or prostatic cancer (148).

Combinations of paclitaxel with other cytotoxic drugs such as cisplatin and doxorubicin show promising results and have to be evaluated further in phase II study designs. Preliminary reports of docetaxel show that it has similar activity as paclitaxel in metastatic breast cancer, platinum-resistant ovarium cancer, non-small cell lung cancer, and pancreatic cancer (Table 5).

Breast Cancer

Paclitaxel showed promising efficacy in the treatment of breast cancer in phase I studies. In several phase II studies in metastatic breast cancer, response rates between 28% and 62% were reported (Table 4).

Paclitaxel (250 mg/m^2) with subcutaneous administration of G-CSF (5μg/kg/day) during a 24-hr infusion as first-line treatment showed the highest response rate (62%) (149). In this trial, prior chemotherapy was not allowed unless in adjuvant setting. Most patients needed dose reduction to 200 mg/m^2 because of severe neutropenia. In another study with minimal pretreated patients (1 prior chemotherapy), a similar response rate (56%, 95% CI: 35–76%) was observed. Responses were correlated with prior chemotherapy (116). Slightly better response rates were seen in patients who had received

Table 4

Phase II Studies of Paclitaxel

Ref.	Tumor type	No. of patients	Dosage in mg/m^2 (infusion time in hr)	Response (%)		Median duration of response	Median survival
				overall	C/P (95% CI)		
157	Ovarian	34	180–250 (24)	20	3/17 (9–38)	12 months	27 months
104	Ovarian	40	110–250 (24)	30	2.5/27.5 (17–47)	6 months	n.r.
170	Ovarian	41	170–175 (24)	36	12/24 (22–53)	n.r.	n.r.
146	Melanoma	28	250 (24)	14	11/3 (4–33)	18 months	n.r.
105	Melanoma	25	250 (24)	12	0/12 (3–31)	11 months	n.r.
149	Breast	25	250 (24)	56	12/44 (35–76)	6+ months	n.r.
147	Kidney	18	250 (24)	0	0 (0–19)	n.r.	n.r.
162	NSCLC	25	200 (24)	24	4/20 (9–45)	27 weeks	40 weeks
163	NSCLC	24	250 (24)	21	0/21 (7–42)	7.5 months	24 weeks
150	Breast	72	200–250 (24)	28[a,b]	0/28 (18–40)	n.r.	n.r.
151	Breast[c]	12	135–150 (24)	25	0/25 (5–57)	n.r.	n.r.
142	SCLC	32	250 (24)	34	0/34 (19–53)	n.r.	n.r.
158	Ovarian	46	135 (n.r.)	11	4/7 (4–24)	n.r.	n.r.
145	UGI[d]	20	250 (24)	5	0/5 (0–25)	n.r.	n.r.
144	Head/neck	30	250 (24)	40	7/33 (23–59)	n.r.	n.r.

n.r., not reported; C, complete; P, partial.

[a]This study reported only the overall response.

[b]Responses to prior chemotherapy: 1 prior chemotherapy: 8/21; 2 prior chemotherapy; 7/22; 3 prior chemotherapy: 5/29.

[c]Three or more prior chemotherapy.

[d]Adenocarcinoma of upper gastrointestinal tract.

adjuvant therapy. A remarkable feature of this study was that 4 of the 6 patients, who were classified as doxorubucin-resistant, responded. Responses were seen at all disease sites.

Several other studies confirmed lack of clinical cross-resistance of paclitaxel with an anthracycline.

In one study, in which 72 patients had been entered on an initial paclitaxel dose of 250 mg/m^2 (250 mg/m^2

Table 5

Preliminary Results of Phase II Studies of Docetaxel

Ref.	Tumor type	No. of patients	Dosage in mg/m^2 (infusion time in hr)	Response (%)	
				Overall	C/P (95% CI)
128	Breast	33	100 (1)	73	18/55 (54–87)
129	Breast	14	100 (1)	57	14/43 (29–82)
130	Breast	21	100 (1)	57	0/57 (34–78)
171	Breast	24	100 (1)	37	8/29 (19–59)
172	Breast	6	100 (1)	66	0/66 (22–96)
165	NSCLC	36	100 (1)	22	0/22 (10–39)
166	NSCLC	20	100 (1)	30	0/30 (12–54)
167	NSCLC	18	100 (1)	28	0/28 (10–53)
126	Ovarian	34	100 (1)	35	6/29 (20–54)
161	Ovarian	20	100 (1)	35	0/35 (15–59)
168	Head/neck	25	100 (1)	44	4/40 (24–65)

C, complete; P, partial.

in case of one prior chemotherapy and 200 mg/m^2 > one prior chemotherapy) in a 24-hr infusion for metastatic breast cancer, 70 patients had prior anthracycline exposure. Thirty-seven patients were considered anthracycline-refractory and 31 patients anthracycline-sensitive. Eleven patients in the anthracycline-refractory group responded (30%, 95% CI 16–47%) and 6 patients in the anthracycline-sensitive group (19%, 95% CI 7.5–37.5%). The overall response was 20% (95% CI 18–40%). Eight of 21 patients with one prior chemotherapy responded (38%, 95% CI 18–62%) and 12 of 51 patients with more than one prior chemotherapy responded (23%, 95% CI 12.5–37%). These results suggest that responses occur equally in both groups between anthracycline-sensitive or anthracycline-resistant disease (150) or between patients pretreated with one or with more than one chemotherapeutic regimen.

In a small group of heavily pretreated patients (more than three prior chemotherapeutic regimens) a response rate of 25% was observed. Starting dose was 135–150 mg/m^2 without G-CSF support depending on pretreatment risk factors (radiotherapy to marrow-bearing bone, prior nitrosoureas) (151).

Most studies were performed with a 24-hr infusion schedule based on the fact of earlier hypersensitivity reactions. The efficacy of paclitaxel administration over 3 hr in patients with metastatic breast cancer was established in a large randomized trial that investigated the activity of paclitaxel on two different doses during a 3-hr infusion schedule (135 mg/m^2 or 175 mg/m^2) in patients with metastatic breast cancer (152). A total of 471 patients were entered in this study. Interim analysis of the first 234 patients showed an overall response of 26%. Thirty-two percent of the patients responded who received only one prior chemotherapy for adjuvant chemotherapy, 20% of those who received chemotherapy for metastatic disease, and 26 percent of patients who had both. Three-hour infusion with premedication allows outpatient treatment. The issue whether the same results were obtained with a long (24-hr) or short (3-hr) term infusion is still under investigation in a European-Canadian center study. Future studies are needed to establish the dose-effect relation of paclitaxel for metastatic breast cancer.

In vitro studies with paclitaxel showed cross-resistance against MDR cell line P388/ADR, which is resistant to anthracyclines (153). From previous phase II studies patients who were considered to have doxorubucin-resistant breast cancer were able to respond to paclitaxel. This indicates that cross-resistance between paclitaxel and doxorubicin may not be complete and that mechanisms of resistance other than MDR may be operational in at least some anthracycline-resistant patients. An ongoing study, at the European Cancer Centre (ECC), investigates to what extent high-dose paclitaxel (starting dose 250 mg/m^2) with granulocyte-colony stimulating factor (G-CSF) support contributes to overcome anthracycline resistance in advanced breast cancer. Seventeen patients have been enrolled in this study so far (154).

Biopsy of 7 patients using immunohistochemistry to study P-glycoprotein expression showed no clear immunoreactivity, indicating that other mechanisms than P-glycoprotein resistance may play a role in resistance against anthracyclines in this study (153). Another study investigates to what extent continuous infusion can overcome MDR. Paclitaxel was administered as a 96-hr continuous infusion in doses ranging from 120 to 160 mg/m^2 in patients with anthracycline-refractory breast cancer. In this study a response rate of 53% (95% CI: 28–77%) was observed (133).

Several phase I studies evaluated the feasibility of clinical relevant doses of the combination therapy of paclitaxel and doxorubicin in minimally pretreated patients with metastatic breast disease (134,155).

In a phase I trial at the M. D. Anderson Cancer Center paclitaxel preceded doxorubicin as a 24-hr infusion at a dose of 125 mg/m^2 directly followed by a 48-hr infusion of doxorubicin at a dose of 60 mg/m^2 with G-CSF (10 μg/kg/day) support starting on day 4 (134). Unexpectedly, the maximum tolerated dose was reached at this first dose step. Stomatitis grade 3 in combination with infection or neutropenic fever was dose-limiting. The investigators had to reduce their doses to 125 mg/m^2 paclitaxel and 48 mg/m^2 doxorubicin. Investigation of the reverse schedule revealed a higher dose of paclitaxel (150 mg/m^2) and doxorubicin (60 mg/m^2). In this schedule neutropenia was dose-limiting. The phase I trial started in the National Cancer Institute investigated paclitaxel and doxorubicin as a concomitant 72-hr infusion (155). In this study both paclitaxel and doxorubicin were escalated. Severe gastrointestinal toxicity developed existing of severe diarrhea and abdominal pain. In 2 patients typhilits (inflammation of the cecum) was documented. The MTDs were paclitaxel:doxorubicin, 160 mg/m^2:75 mg/m^2 and 180 mg/m^2:60 mg/m^2.

The Indiana University study investigates the sequence dependency of paclitaxel and doxorubicin. Doxorubicin was administered as a rapid i.v. injection and paclitaxel as a 24-hr continuous infusion. A 4-hr interval between the administration of both drugs was inserted. Each patient served as his or her own control.

Grade 3/4 mucositis occurred when paclitaxel (175 mg/m^2) preceded doxorubicin (60 mg/m^2). Based on this pilot study, it can be concluded that the occurrence of mucositis appears depending on the order of administration (156). Phase III trials are needed to investigate the efficacy of the combination therapy over single-agent therapy. The ECOG in cooperation with the NCCTG and SWOG started a phase III trial with three arms: arm I, single-agent paclitaxel 175 mg/m^2 during a 24-hr infusion; arm II, single-agent doxorubicin 60 mg/m^2; arm III, the combination doxorubicin 50 mg/m^2 i.v. push injection and paclitaxel 150 mg/m^2 as a 24-hr infusion.

Docetaxel has shown to induce responses in doxorubicin-resistant metastatic breast cancer patients as well. Preliminary results from a phase II trial showed that 9 of 15 patients responded (60%, 95% CI 32–84%). Phase II trials were started at doses of 100 mg/m^2 by 1-hr infusion repeated every 3 weeks (Table 5). In all studies patients were only minimally pretreated or had one prior chemotherapy. The response rates were very high (57–73%). These impressive response rates make docetaxel one of the most active agents against breast cancer. The results of studies with larger numbers of patients are to be awaited before firm conclusions can be drawn.

Ovarian Cancer

Interest and enthusiasm for paclitaxel arose when, in a phase I study, 1 heavily pretreated patient with platinum refractory ovarian cancer had a prolonged complete response. Several phase II studies showed activity of paclitaxel in heavily pretreated or platinum-resistant patients (105,157,158). This indicates that paclitaxel does have effects in situations where standard chemotherapy is relatively ineffective. In these phase II studies paclitaxel was administered as a 24-hr infusion every 21 days. The initial starting dose was 250 mg/m^2 for patients who had received more than one chemotherapeutic regimen. Dose reduction was carried out in all patients because of poor bone marrow reserves: 170 mg/m^2 and 135 mg/m^2 were the recommended doses for the patients who had received one and more than one cisplatin-containing chemotherapeutic regimens, respectively. Response rates in these phase II studies have varied between 20 and 36%. Responses were equally distributed among platinum-sensitive and platinum-resistant patients (157).

A large four-arm factorial randomized study, comparing high (175 mg/m^2) versus low dose (135 mg/m^2) and short (3 hr) versus long infusion (24 hr), was started in 1991 to evaluate the safety of a shorter infusion and a potential dose-response relation in ovarian cancer patients (102). Interim analysis on 293 evaluable patients showed a slight advantage in response for the 175 mg/m^2 treatment arm over the 135 mg/m^2 arm (22% versus 16%, $p = 0.1$). There was no clear advantage for the 24-hr infusion schedule over the 3-hr infusion schedule (20% versus 19%, $p = 0.8$). There was, however, a slight advantage in the progression-free survival for the dose 19 weeks for the 175 mg/m^2 infusion schedule and 14 weeks for the 135 mg/m^2 infusion schedule ($p = 0.001$). This is the first randomized study that demonstrates a dose-response relation for ovarian cancer. The 3-hr infusion achieves efficacy results that are at least equivalent to the 24-hour infusion schedule. The 3-hr infusion 175 mg/m^2 offers the best therapeutic index in this randomized trial. In a large study with heavily pretreated platinum-refractory ovarian cancer, paclitaxel (135 mg/m^2) was administered as a 24-hr infusion (159). At this low dose level many patients experienced severe neutropenia (43%), sometimes associated with fever. In 1.5% of the cases sepsis occurred. The response rates are comparable with those of other studies. In this study the performance status was associated with a higher response rate. Responders had a median time to progression of 7 months while for nonresponders it was 4 months, and there seems evidence of clinical benefit from paclitaxel therapy.

In a phase I trial with G-CSF support (10 μg/kg/day), doses were escalated from 170 to 300 mg/m^2 (113). In this study patients had received up to two prior chemotherapeutic regimens. Fourteen patients were evaluable for response (11 were presumed platinum-resistant), and 5 major responses (1 CR and 4 PR) and 5 minor responses were observed. All responders were in the platinum-resistant group. No long-term follow-up was done. The recommended dose for phase II studies was 250 mg/m^2, with G-CSF (113).

A phase I trial with i.p. administration of paclitaxel was initiated to increase the exposure of tumor in the abdominal cavity to the drug and at the same time to reduce systemic uptake and toxicity (57). Twenty-five patients with histologically proven residual disease in the peritoneal cavity were entered in this study. All patients were heavily pretreated and did not respond to standard therapy. Two patients responded with disappearance of ascites due to paclitaxel treatment and 4 patients had reduction of serum CA-125 levels. The clinical and laboratory responses were, however, of short duration (<6 months). One patient remained stable for more than 1 year. Phase II studies are currently being undertaken to determine the actual response rate for this treatment.

Paclitaxel as first-line treatment was investigated by the GOG in a randomized phase III trial comparing the efficacy between paclitaxel/cisplatin (135/75 mg/m^2) and the standard treatment cisplatin/cyclophosphamide (75/750 mg/m^2). Higher response rates for the paclitaxel/cisplatin regimen above the standard arm (79% versus 63%) were reported. The median duration of progression-free interval was 14 months for the cisplatin/cyclophosphamide arm compared to 18 months for the paclitaxel/cisplatin arm. Survival analysis must be awaited before cisplatin/paclitaxel can be regarded as the first-line therapy for ovarian cancer (160).

The data indicate that paclitaxel is, however, not a curative agent in the treatment of ovarian carcinoma but may be extremely valuable for palliative treatment, with a response duration of about 1 year with minimal pretreatment and 6 months for heavily pretreated patients.

Results of phase I studies suggest that docetaxel has the same antitumor profile as paclitaxel. In phase II studies docetaxel (100 mg/m^2) was administered as a 1-hr infusion. These studies confirmed docetaxel activity against platinum-refractory ovarian cancer patients (126,161,173).

Non-Small Cell Lung Cancer

Paclitaxel has been studied in two phase II trials of patients with non-small cell lung cancer (NSCLC) (162, 163). In both studies paclitaxel was administered as a 24-hr infusion. Cycles were repeated every 3 weeks. In the first study three new agents (paclitaxel, merbarone, and piroxantrone) were investigated in a randomized phase II trial (163). The paclitaxel dose was 250 mg/m^2. Only stage IV disease was allowed. The other study included patients with stage IIIB and IV disease. Paclitaxel dosage was 200 mg/m^2 here (162). Response rates were 21% (95% CI: 7–42%) and 24% (95% CI: 9–45%), respectively. These two phase II studies show that paclitaxel is one of the most active chemotherapeutic agents in NSCLC.

Combination therapies with carboplatin and cisplatin are under investigation. A sequence-finding study with carboplatin and paclitaxel is under investigation by the ECC (164).

Preliminary results from three phase II studies of docetaxel (dose: 100 mg/m^2) administered in 1 hr and repeated every 3 weeks show the same activity as paclitaxel (165–167).

Head and Neck Cancer

High activity of paclitaxel was observed by the Eastern Cooperative Oncology Group (ECOG) for squamous cell carcinoma of the head and neck (144). They performed a study of paclitaxel dose of 250 mg/m^2 with G-CSF (5μg/kg/day) support during a 24 hr infusion repeated every 3 weeks. A total of 34 patients, with good performance status (ECOG 0-1), were entered into this study; 32 patients had recurrent disease and 2 patients were newly diagnosed. Only 4 patients received cisplatin-based chemotherapy. Twelve patients had a major response (40%, 95% CI: 23–59%); figures for the median duration of response are not yet available. Severe neuropathy was observed in 3 patients, and these results were the same as mentioned with other studies which used 250 mg/m^2 paclitaxel with G-CSF support as a 24-hr infusion (116,163). However, excessive alcohol abuse is common in the patient with head and neck cancer, which could be a predispositing factor for the development of sensory neuropathy in patients who receive high-dose paclitaxel ($\geq$250 mg/m^2).

The European Organization for Research and Treatment of Cancer (EORTC) will start a randomized phase III trial to compare paclitaxel 175 mg/m^2 to methotrexate 40 mg/m^2. This study will address the issue of paclitaxel efficacy over the standard treatment with methotrexate. The M. D. Anderson Cancer Center started a phase I trial of paclitaxel during a 24-hr infusion plus low-dose methotrexate. The Johns Hopkins Oncology Center evaluates in a phase II trial the combination therapy consisting of paclitaxel 175 mg/m^2 during a 24-hr infusion in combination with continuous infusion during 3 days of ifosfamide/mesna (5 g/3days) in patients with recurrent disease, with or without prior cisplatin exposure. Patients in this trial without prior cisplatin will continue after progression on the paclitaxel-based chemotherapy with cisplatin/ 5-fluorouracil. The ECOG is investigating in a randomized phase II trial the efficacy of high-dose (200 mg/m^2; 24-hr infusion) versus low-dose paclitaxel (135 mg/m^2; 24-hr infusion) in combination with cisplatin.

Pilot studies for combination therapy include carboplatin, cisplatin with 5-fluorouracil, and different infusion schedules including 3-hr and a 10-day continuous infusion. Docetaxel also showed a high level of activity against head and neck cancer. Forty-two patients were treated with 100 mg/m^2 during a 1-hr infusion. Eleven of 25 evaluable patients had a major response (44%, 95% CI: 24–65%), although 4 patient responses were not yet confirmed in this preliminary report (168).

Esophageal Cancer

Preliminary results from a phase II study suggest substantial activity of paclitaxel in esophageal cancer.

Paclitaxel with G-CSF support (5 μg/kg/day) was administered at a dosage of 250 mg/m^2 as a 24-hr infusion repeated every 3 weeks. Twelve of 42 patients showed a partial response (29%, 95% CI: 16–45%), although responses were very brief. Responses were equally distributed among epidermoid carcinoma and adenocarcinoma. Combination therapies are underway with cisplatin and 5-fluorouracil (144).

CONCLUSIONS AND PERSPECTIVES

Paclitaxel is a novel antineoplastic agent with a unique mechanism of action. Side effects are moderate. Neutropenia and sensory neuropathy were found to be the major dose-limiting toxicities in phase I trials using paclitaxel as single agent. In dose-escalating studies with G-CSF, sensory neuropathy is dose-limiting. In one study neuromuscular toxicity is dose-limiting when paclitaxel is combined with cisplatin and G-CSF. Hypersensitivity reactions frequently occurred. It is, however, not clear whether these reactions were evoked by paclitaxel or by its excipient Cremophor EL®. Extensive premedication reduces the severity and frequency of this event.

Phase II trials showed that paclitaxel has significant activity in advanced ovarian carcinoma, metastatic breast cancer, head and neck cancer, esphageal cancer, and NSCLC. Paclitaxel even produced responses in platinum-resistant ovarian carcinoma and doxorubicin-resistant breast carcinoma. In addition, preliminary phase I trials of paclitaxel combined with cisplatin have also shown objective responses in several neoplasms. Docetaxel, a semisynthetic analog of paclitaxel, has twice the potency of paclitaxel in preclinical studies and has an apparently identical mechanism of action. In preliminary reports docetaxel demonstrated extremely high activity in metastatic breast cancer. Response rates for ovarian carcinoma and non-small cell lung cancer were similar to those for paclitaxel. As with paclitaxel, leukoneutropenia is the major dose-limiting factor. Besides myelosuppression, cumulative edema and effusion are seen as side effects after docetaxel administration. These toxic effects have a cumulative character and constitute important issues to be dealt with for further development of docetaxel treatment.

Perspectives

Taxanes are an important new group of antineoplastic agents. In the near future investigations have to be done in several fields. First, adequate supplies of paclitaxel are needed. This may be accomplished by the production of semisynthetic paclitaxel from 10-deacetylbaccatin III precursor or large-scale production by fungal species. Other possibilities are the use of second-generation agents like docetaxel or other semisynthetic analogs.

Second, the current pharmaceutical i.v. formulations containing ethanol and Cremophor EL® for paclitaxel and polysorbate 80 for docetaxel are not optimal. Potential side effects of the vehicle in which paclitaxel is administered could be avoided by the development of paclitaxel analogs that have a higher water solubility.

Third, identification of paclitaxel metabolites and their potential role in toxicity or activity in several malignancies should be investigated. Trials are needed to evaluate drug interactions, which may influence hepatic metabolism, for example drugs that interfere with the cytochrome P-450 enzyme system. Pharmacokinetic studies of paclitaxel in patients with hepatic impairment are needed to define the appropriate dosage in this group.

Fourth, studies are needed to investigate the dose-response relationship, the roles of dose intensification in patients with several malignancies and of prolonged infusion to circumvent drug resistance.

Fifth, perspectives in clinical research could be the development of combination trials of paclitaxel with other antineoplastic agents or biochemical modulators. In addition, sequence-finding studies with carboplatin are ongoing in non-small cell lung cancer and ovarian cancer. Furthermore, high-dose paclitaxel is administered to try to overcome anthracyline resistance in breast cancer. These trials are ongoing in Europe.

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